Pathophysiology

Pseudotumor cerebri syndrome often occurs from impaired cerebrospinal fluid (CSF) absorption by the arachnoid granulations. This results in elevated intracranial pressure (ICP) within the ventricles and around the cerebral convexities. The reason for the absence of ventricular enlargement is unknown. Increased brain water content may decrease brain compliance, resulting in normal-size ventricles, despite elevated CSF pressure. However, this explanation is speculative. Increased CSF production by the choroid plexus may be a component of the etiology of some cases of pseudotumor cerebri.

Conditions associated with pseudotumor cerebri are listed in Table 89-1. The association is well established, and the pathogenesis is well delineated for some of these conditions. For example, with vitamin A toxicity, unbound serum or CSF vitamin A damages the arachnoid granulations, resulting in decreased CSF drainage through the granulations. Dural sinus thrombosis and arteriovenous sinus shunts cause pseudotumor cerebri by elevating the intracranial venous pressure. Increased pressure within the venous sinuses reduces the pressure gradient across the arachnoid granulations, resulting in decreased CSF drainage through the granulations.

The role of some of the other associated conditions (see Table 88-1) in the pathogenesis of pseudotumor cerebri is speculative. Although corticosteroid withdrawal, nalidixic acid use, tetracycline use, head trauma, and renal failure are associated with pseudotumor cerebri, the mechanisms by which these associated conditions elevate ICP are unknown. Some conditions, such as oral contraceptive use, may be spurious associations and not a true cause of pseudotumor cerebri.

Epidemiology

Pseudotumor cerebri most frequently occurs in obese women of childbearing age. In adults, the syndrome is often idiopathic. The relationship of female gender and obesity to the pathophysiology of idiopathic cases is unknown. Vitamin A may contribute to the etiology of these cases. Obesity and female gender may be associated with elevated serum or CSF vitamin A levels, resulting in damage to the arachnoid granulations. Alternatively, female gender and obesity may be associated with...
increased intracranial venous pressure, which causes a reduction of the pressure gradient across the arachnoid granulations, resulting in decreased CSF drainage, as described previously.

Among prepubescent children and infants, there is no gender predominance, and obesity occurs less frequently compared with adults. Associated causes (see Table 89-1) are common in children and are identified in approximately 50% of cases. After puberty, the clinical profile of children with pseudotumor cerebri is similar to that of adults.

Clinical Evaluation

Clinical Symptoms

The presenting clinical symptoms are from elevated ICP and are listed in Table 89-2. Headaches, sometimes associated with nausea and vomiting, are common. These headaches are often worse in the morning and may be exacerbated by coughing, sneezing, or lying flat. Pulsatile tinnitus is common in adults and older children. It may be unilateral or bilateral and is synchronous with the heartbeat. The tinnitus is attributed to intracranial vascular pulsations transmitted by CSF under high pressure to the walls of the venous sinuses. This creates pulsatile turbulent flow in the venous sinuses that is experienced by the patient as pulsatile tinnitus.

Decreased vision and diplopia are common presenting symptoms in children. Transient visual obscurations (TVOs) are common in older children and adults. TVOs are characterized by partial or complete visual loss in one or both eyes and are often associated with postural changes. They typically have a duration of < 30 seconds and may occur several hundred times in one day. Transient visual obscurations are a nonspecific symptom of disk edema and are probably related to transient optic nerve head ischemia.

Younger children and infants are often unable to verbalize the symptoms noted above. They frequently present with nonspecific symptoms such as irritability, fatigue, somnolence, dizziness, apathy, and decreased appetite. Strabismus observed by physicians or parents in an asymptomatic child may be the presenting complaint. Similarly, papilledema noted on a routine examination in an asymptomatic child may prompt referral.

Clinical Signs

The clinical signs of pseudotumor cerebri are attributable to elevated ICP. The most common signs are papilledema and oculomotor nerve palsies. Papilledema is less frequent in infants with pseudotumor cerebri and open cranial sutures.

Papilledema

Papilledema and disk edema are separate terms that are often used incorrectly. Disk edema is a sign of pathologic insult to the optic nerve head. Pathologic insults may be compressive, inflammatory, ischemic, or metabolic. These insults cause decreased axoplasmic flow and result in the intra-axonal accumulation of material at the optic nerve head. This is seen clinically as disk elevation, peripapillary opacification of the nerve fiber layer, and obscuration of the disk borders and disk vessels. Swollen axons at the optic nerve head secondarily compress the central retinal vein, resulting in loss of spontaneous venous pulsations, optic disk hyperemia, vessel tortuosity, flame hemorrhages, and cotton-wool spots.

Papilledema specifically refers to disk edema from elevated ICP. Elevated ICP is transmitted via the subarachnoid space to the optic nerve head. The elevated pressure at the optic nerve head causes local ischemia, resulting in disk edema and the clinical signs noted above. Papilledema cannot be distinguished from other causes of disk edema by the appearance of the optic nerve head. However, there are two clinical characteristics that suggest (but do not prove) elevated ICP as the cause of disk edema: bilaterality and intact visual acuity.
**TABLE 89-2. Presenting Symptoms of Pseudotumor Cerebri**

<table>
<thead>
<tr>
<th>Headaches</th>
<th>Retrobulbar pain</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Pulsatile tinnitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient visual obscurations</td>
<td>Blurry vision</td>
<td>Diplopia</td>
<td>Photophobia</td>
<td>Strabismus noted by the parents</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Neck pain and stiffness</td>
<td>Irritability</td>
<td>Somnolence</td>
<td>Nervousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apathy</td>
<td>Dizziness</td>
<td>Myalgias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shoulder and back pain</td>
<td>Paresthesias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreased appetite</td>
<td>Ataxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Papilledema noted on routine exam of asymptomatic patient</td>
<td></td>
</tr>
</tbody>
</table>

- **Bilaterality**: Elevated ICP is transmitted to both optic nerve heads and typically causes bilateral disk edema. However, bilateral asymmetric papilledema and unilateral papilledema occasionally occur.

- **Intact visual acuity**: Visual acuity is generally normal in acute papilledema. However, chronic papilledema may ultimately result in decreased visual acuity.

Thus, papilledema should be suspected in a patient with intact visual acuity and bilateral disk edema. However, elevated ICP must ultimately be confirmed by lumbar puncture before attributing disk edema to elevated ICP.

Chronic papilledema may result in gradual progressive axonal death. Clinically, the optic nerve head appearance changes from hyperemic papilledema to a pale swollen disk without hyperemia. As more axons die, disk swelling decreases, resulting in a pale, atrophic optic nerve head. These changes typically occur over several months. However, in severe cases, acute papilledema may progress to optic nerve pallor in several weeks.

**Visual Function**

Papilledema initially causes visual field loss in patients with pseudotumor cerebri. Although visual fields deficits are common, patients are often not aware of visual dysfunction during the early course of their disease. Enlargement of the blind spot is the most common visual field deficit. The physiologic blind spot is located about 12° to 15° temporal to fixation and is approximately 5° in size. With disk edema, the blind spot may be enlarged to 20° or more in size. The enlarged blind spot occurs from mechanical displacement of the peripapillary retina by a swollen optic disk and does not represent optic nerve dysfunction. Other common visual field deficits occur from optic nerve dysfunction. These include peripheral constriction, inferonasal steps, arcuate deficits, and depression of the nasal visual fields.

Visual acuity is typically spared until late in the disease course. Patients with chronic papilledema are at risk for progressive visual field deficits that may ultimately affect the central visual field, resulting in decreased visual acuity. Patients with decreased visual acuity typically have severe peripheral visual fields deficits and optic nerve pallor.

Color vision is also preserved until late in the disease course and is therefore an insensitive parameter for early visual loss. Relative afferent pupillary defects are sensitive signs of asymmetric optic nerve dysfunction. However, many patients with pseudotumor cerebri have bilateral optic nerve dysfunction and therefore do not have a relative afferent pupillary defect.

**Oculomotor Nerve Palsies**

Elevated ICP from any cause may shift the brainstem and stretch cranial nerve VI, resulting in a cranial nerve VI palsy. Cranial nerve VI palsies are common in children with pseudotumor cerebri. They may be unilateral or bilateral and are generally incomplete. Cranial nerve VI palsies due to pseudotumor cerebri generally resolve with normalization of ICP.

Children with pseudotumor cerebri may have other oculomotor abnormalities, including cranial nerve IV palsy, cranial nerve III palsy, cranial nerve VII palsy, skew deviation, and acute comitant esotropia (crossed eyes with no limitation of abduction to suggest a cranial nerve VI palsy). These other oculomotor deficits are uncommon and should be attributed to pseudotumor cerebri only if they resolve with normalization of the ICP and other causes are ruled out.

**Diagnosis**

Evaluation of a child with bilateral disk edema is a medical emergency. A thorough history should be obtained from the child and the parents. The symptoms noted in Table 89-2 should be addressed. Many patients will not volunteer a description of symptoms, such as pulsatile tinnitus or transient visual obscurations, unless the physician specifically inquires about these entities. The parents of infants should be questioned regarding the presence of irritability, somnolence, anorexia, and strabismus. The past medical history should identify medical conditions and medications that may be associated with pseudotumor cerebri (see Table 89-1). Specific associations that should be addressed include recent ear infections, antibiotic
treatment, and vitamin A consumption. Adolescents with acne may be treated with vitamin A or isotretinoin. Systemic and topical treatment of acne with vitamin A compounds has been associated with pseudotumor cerebri.

A detailed ophthalmologic examination is essential. The visual acuity of each eye should be documented, if possible. Visual acuities with picture symbols can be obtained in children as young as 3 years of age. Quantitative visual fields are essential to identify early signs of visual dysfunction and may be obtained in children as young as 5 years of age. Color vision deficits indicate severe visual dysfunction and should be documented. Ocular motility examination may reveal cranial nerve VI palsies and, less commonly, other oculomotor nerve palsies. A dilated fundus examination and stereoscopic disk photographs allow the detection and documentation of disk edema. Infants with open cranial sutures and bulging fontanelles may not have papilledema, despite the presence of elevated ICP.

Neuroimaging should be obtained emergently to rule out an intracranial mass and hydrocephalus. Magnetic resonance imaging (MRI) of the brain and orbits with gadolinium is the ideal imaging modality. MRI is superior to computed tomography for evaluation of the venous sinuses and will identify most cases of cerebral venous sinus thrombosis. Venous sinus thrombosis should be suspected in patients with a history of recent ear infections, multiple miscarriages, oral contraceptive use, and known coagulopathies, and in patients presenting in the postpartum period. Magnetic resonance venography should be considered for the evaluation of these patients.

MRI may reveal subtle signs suggestive of elevated ICP in patients with pseudotumor cerebri. These signs include flattening of the posterior sclera, empty sella, enhancement of the prelaminar optic nerve, distortion of the peripapillary subarachnoid space, vertical tortuosity of the orbital optic nerve, and intraocular protrusion of the prelaminar optic nerve.

If neuroimaging rules out an intracranial mass and hydrocephalus, a lumbar puncture should be obtained to rule out intracranial infections and malignancy to confirm elevated ICP. The ICP should be measured with the patient in the lateral decubitus position with the legs relaxed. Sedation is often necessary in children. The ICP is considered elevated if it is above 200 mm H2O for nonobese patients and above 250 mm H2O for obese patients. CSF studies should include protein, glucose, cell count, bacterial cultures, fungal cultures, Mycobacterium tuberculosis cultures, and cytology. Older children may report that their symptoms of elevated ICP improve after the lumbar puncture. Improvement of symptoms such as headaches, nausea, vomiting, and pulsatile tinnitus after the lumbar puncture supports elevated ICP as the etiology for these symptoms.

Pseudotumor cerebri is diagnosed if neuroimaging shows normal or small ventricles, no intracranial mass, and if the lumbar puncture is normal except for elevated ICP. Blood tests may reveal conditions associated with pseudotumor cerebri, such as anemia, hypocalcemia, renal failure, and vitamin A toxicity. It is reasonable to obtain a complete blood count, electrolytes, serum calcium and phosphate levels, blood urea nitrogen, serum creatinine, antinuclear antibodies, serum vitamin A levels, and a urinalysis. Hypercoagulability testing should be obtained in patients with venous sinus thromboses of unknown cause.

**Differential Diagnosis**

Pseudopapilledema is a congenital disk anomaly that simulates papilledema. It is characterized by an elevated optic nerve head, which may contain optic nerve head drusen. Patients with pseudopapilledema may have TVOs and visual fields deficits similar to patients with true papilledema. Pseudopapilledema is differentiated from true disk edema by the absence of nerve fiber layer opacification, disk hyperemia, obscuration of the disk vessels, and cotton-wool spots. Patients with pseudopapilledema have normal ICP. However, the identification of pseudopapilledema on physical examination should obviate the need for neuroimaging and lumbar puncture.

Infiltrative central nervous system (CNS) malignancies may present with a pseudotumor cerebri syndrome. These “masquerade syndromes” include gliomatosis cerebri and primitive neuroectodermal tumors. Patients with these entities may initially have normal MRI and normal CSF studies, except for elevated ICP. They typically develop progressive cranial nerve deficits, and repeat MRI later in the disease course will reveal the tumor. Therefore, patients diagnosed with pseudotumor cerebri who develop progressive cranial nerve deficits should have repeat MRI.

**Prognosis**

Visual loss from papilledema is the major morbidity from pseudotumor cerebri. The disease course is chronic in adults, and permanent visual loss is common. The disease appears to be more self-limited in children, with frequent spontaneous remissions, although recurrent disease has been described. Children are also at risk for severe permanent visual loss. Therefore, visual function and optic nerve appearance should be monitored in children with pseudotumor cerebri until papilledema resolves. Quantitative perimetry is the most sensitive test for the detection of visual loss from papilledema and should be obtained when possible. Decreased visual acuity and color vision loss are signs of advanced disease.
The recommended frequency of examinations varies, depending on the visual function status, the level of ICP, and the current treatment. Examinations initially should be scheduled weekly in a patient with severe optic neuropathy. Bimonthly examinations are generally adequate for patients with normal visual function.

Unfortunately, visual function tests cannot be obtained in infants and young children. Visual evoked response testing remains normal until severe optic nerve damage has occurred. Therefore, this test has no role in monitoring children with pseudotumor cerebri.

**Treatment**

Asymptomatic patients with normal visual function may be monitored without specific treatment. Associated conditions should be identified and treated. Medications associated with pseudotumor cerebri should be discontinued, if possible. Obese patients should be encouraged to lose weight, and referral to a dietician should be considered. Headaches may respond to tricyclic antidepressants or nonsteroidal antiinflammatory drugs.

Medications that lower ICP are indicated for patients with headaches and/or mild visual field deficits. CSF production by the choroid plexus is dependent on carbonic anhydrase. Diamox® (acetazolamide) inhibits carbonic anhydrase and therefore lowers ICP by reducing the rate of CSF formation. A dose of 1 to 4 g/d in two or three divided doses is indicated for adults (5 mg/kg four times daily for children). Unfortunately, side effects are common and include paresthesias, unpleasant taste to carbonated beverages, altered taste of food, and a low serum bicarbonate level. Less common side effects include allergic reactions, renal stones, and aplastic anemia. Diamox® contains sulfa and should not be used in patients who are allergic to sulfa. Electrolytes and a complete blood count should be monitored every several months in patients treated with this drug.

Lasix® (furosemide), a weak carbonic anhydrase inhibitor and chloride reuptake blocker, also reduces CSF formation at the choroid plexus and may be used in patients who are unable to tolerate Diamox®. Alternatively, Lasix® may be combined with Diamox®, although increased effectiveness with this combination is not proven. Corticosteroids may rapidly lower ICP. However, chronic treatment with corticosteroids is associated with numerous side effects, and increased ICP may occur with cortico-steroid withdrawal. Therefore, treatment with cortico-steroids should generally be avoided.

Repeat lumbar punctures are not an effective treatment. A lumbar puncture lowers ICP for only several hours, as the entire CSF volume is renewed approximately four times a day.

Surgery is indicated for patients at risk for severe visual loss. Thus, indications for surgery include:

- Progressive visual loss despite maximum-tolerated medical treatment
- Severe visual loss at presentation
- Severe papilledema or chronic atrophic papilledema, especially in children who are too young to perform reliable visual field testing

Surgical options include optic nerve sheath fenestration (ONSF) and lumbar peritoneal (LP) shunt. These procedures rapidly reduce papilledema, although complete resolution may take several weeks.

ONSF involves making multiple slits in the perioccipital meninges behind the globe. This allows the egress of CSF through the perioccipital nerve sheath and reduces pressure at the optic nerve head. ONSF effectively treats papilledema, stabilizing or improving visual function in children with visual loss from pseudotumor cerebri. Unilateral ONSF will eliminate papilledema of both disks in approximately 50% of cases and reduce headache symptoms in some patients. Complications, including ischemic optic neuropathy, transient blindness, pupillary dilation, and retrobulbar hemorrhage, are infrequent. However, there is a high rate of failure with long-term follow-up.

LP shunting reduces ICP and therefore treats the headaches and relieves the pressure on both optic nerves. This procedure effectively resolves papilledema and stabilizes vision in children with visual loss from pseudotumor cerebri. However, low-pressure headaches associated with an acquired Arnold-Chiari malformation type I tonsillar herniation may occur. Shunt failures are frequent, and the procedure may need to be repeated many times over several years. Other complications include shunt infections, abdominal pain, CSF leak, and migration of the peritoneal catheter.

ONSF should be considered for patients with progressive visual loss after apparently successful LP shunting. Similarly, an LP shunt should be considered for patients with progressive visual loss after an ONSF.

Bariatric surgery effectively reduces ICP in severely obese patients with pseudotumor cerebri and has the added advantage of reducing comorbidity associated with excessive weight. Although bariatric surgery is most commonly performed on adults, it has been used to treat severely obese adolescents. The weight loss and reduction of ICP occurs gradually over several months. Therefore, this is not the treatment of choice for patients with acute visual deterioration.

**Discussion**

The diagnosis and treatment of children with pseudotumor cerebri requires collaboration among pediatricians, neurologists, and ophthalmologists. Associated conditions must be...
recognized and treated. The integrity of the visual system should be evaluated by an ophthalmologist. Careful follow-up of visual function and aggressive treatment of progressive or severe visual loss should minimize morbidity.

Acknowledgment

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Suggested Readings


Practitioner and Patient Resources

American Academy of Ophthalmology
P.O. Box 7424
San Francisco, CA 94120-7424
Phone: (415) 561-8500
http://www.aao.org

The mission of the American Academy of Ophthalmology is to advance the lifelong learning and professional interests of ophthalmologists to ensure that the public can obtain the best possible eye care. The Web site also contains information for patients and the public.

Lighthouse International
111 East 59th Street
New York, NY 10022
Phone: (212) 821-9200
http://www.lighthouse.org

Lighthouse International is a leading resource worldwide on vision impairment and vision rehabilitation. Through its pioneering work in vision rehabilitation services, education, research, and advocacy, Lighthouse International enables people of all ages who are blind or partially sighted to lead independent and productive lives.

National Federation of the Blind (NFB)
1800 Johnson Street, Suite 300
Baltimore, MD 21230-4998
Phone: (410) 659-9314
http://www.nfb.org

The purpose of the NFB is two-fold—to help blind persons achieve self-confidence and self-respect and to act as a vehicle for collective self-expression by the blind. By providing public education about blindness, information and referral services, scholarships, literature and publications about blindness, aids and appliances and other adaptive equipment for the blind, advocacy services and protection of civil rights, development and evaluation of technology, and support for blind persons and their families, members of the NFB strive to educate the public that the blind are normal individuals who can compete on terms of equality.

Prevent Blindness America
500 East Remington Road
Schaumburg, IL 60173
Phone: 800-331-2020
http://www.preventblindness.org

Focused on promoting a continuum of vision care, Prevent Blindness America touches the lives of millions of people each year through public and professional education, certified vision screening training, community and patient service programs, and research.